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Telemedically Supported Case Management of Living-Donor Renal Transplant Recipients to Optimize Routine Evidence-Based Aftercare: A Single-Center Randomized Controlled Trial

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Improving mid-term and long-term outcomes after solid organ transplantation is imperative, and requires both state-of-the-art transplant surgery and optimization of routine, evidence-based aftercare. This randomized, controlled trial assessed the effectiveness of standard aftercare versus telemedically supported case management, an innovative aftercare model, in 46 living-donor renal transplant recipients during the first posttransplant year. The model includes three components: (i) chronic care case management initiated after discharge, (ii) case management initiated in emerging acute care situations, and (iii) a telemedically equipped team comprising a transplant nurse case manager and two senior transplant physicians (nephrologist, surgeon). Analyses revealed a reduction of unplanned inpatient acute care, with considerable cost reductions, in the intervention group. The prevalence of nonadherence over the 1-year study period was 17.4% in the intervention group versus 56.5% in the standard aftercare group ($p = 0.013$). Only the intervention group achieved their pre-agreed levels of adherence, disease-specific quality of life, and return to employment. This comparative effectiveness study provides the basis for multicenter study testing of telemedically supported case management with the aim of optimizing posttransplant aftercare. The trial was registered with the German Clinical Trials Register (www.DRKS.de), DKRS00007634.

Abbreviations: ALL, Fragebogen Alltagsleben (Questionnaire of Daily Living); ATS, ANOVA-type statistic; BAASIS®, Basel Assessment Adherence to Immunosuppression Scale; BSI-18, Brief Symptom Inventory 18; CAS, composite adherence score; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DGCC, German Association for Care and Case Management; DRG, diagnosis-related group; ESRD-SCL™, End-Stage Renal Disease Symptom Checklist-Transplantation Module; IQR, interquartile range; RTR, renal transplant recipient; SOCG, standard of care group; STP, senior transplant physician; TNCM, transplant nurse case manager; TSCMG, telemedically supported case management group; T, time point; TX, Transplantation; UMC, University Medical Center

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Introduction

The organ shortage crisis in Germany has led to an average waiting time for deceased donor kidney transplants of approximately 10 years. This situation demands alternative solutions. Living-donor renal transplantation has become an important focus at the University Medical Center (UMC) Freiburg. Attaining the best possible mid-term and long-term outcomes for renal transplant recipients (RTR), however, requires both state-of-the-art surgery and optimization of routine evidence-based aftercare—a complex challenge.

Promoting adherence within a tailored approach is a key requirement. Following the development of various chronic disease self-management (1) and case management (2) approaches for chronic conditions in general, De Geest et al. (3) went one step further and advanced the concept of chronic illness management for transplant recipients. To date, only a small number of

structured programs for RTR have been described, mainly focused on self-management (4–7). Case management solves complex, intrapersonal, interpersonal, and environmental concerns. According to criteria set out by Klie (8), case management is advisable in the first year posttransplant, involving various sectors and healthcare providers, and demanding high standards of care continuity and patient participation. Advanced levels of patient self-responsibility, self-care, and self-management are required, but it is recognized that this may not be achievable for RTRs. Dew et al. detected a high prevalence of nonadherence (35.6%) in this setting (9), and De Geest et al. (10) observed that 16–36% of graft losses are associated with nonadherence, a finding confirmed elsewhere (11–14).

The benefit of telemedicine for delivering effective care coordination in chronic disease conditions has been confirmed in settings such as cardiac insufficiency. Video technology is efficient. Evidence for remote telemonitoring with no human involvement is scarce and, instead, the combination of both remote and personal contact is likely to ensure earlier treatment in response to deterioration (15–18). Consequently, the UMC Freiburg designed a telemedically supported aftercare project in cooperation with the UMC Strasbourg, France, which was funded by the European Union within the framework of the INTERREG IV Oberrhein program (19). Technical equipment and services were shared. However, the nature of aftercare necessarily differed between the French liver and German kidney transplant recipients. Due to limited resources, the Freiburg project was offered only to living-donor RTR, justified because of the higher need to avoid nonadherence (12,14,20). Complete adherence to the immunosuppressive regimen and self-care is crucial. To support this, our priority was to achieve daily patient participation in remote telemonitoring, rather than patient "control." Therefore, we did not plan electronic monitoring of immunosuppressant intake via telemedical equipment. Schäfer-Keller et al. (21) have proposed an alternative measurement method using a composite adherence score (CAS) that provides acceptable sensitivity (72%) and accuracy (42%) when compared to electronic monitoring.

Video consultations may not only help to detect deterioration promptly, but also enable patients to explain and discuss barriers to full adherence. Telemedically supported case management could transform posttransplant aftercare if it provides instant delivery of tailored services, even for more complex clinical challenges. This could potentially lower the risk for acute complications or graft rejection and the associated need for medical service utilization. We hypothesized that this approach would support stable adherence with improved quality of life and quasi-normal living, promoting better long-term outcomes.

Materials and Methods

Study design

This was a prospective, open-label, randomized comparative effectiveness study that used a repeated-measures design (19,22). The Ethics Committee of the Albert-Ludwigs-University Freiburg, Germany (608/14) approved the study protocol.

All adult living donor RTRs at the UMC Freiburg were eligible. After written, informed consent to a concealed allocation to either standard or interventional aftercare, literate German speakers with the ability to take medication independently were included. Randomization was then performed using a computer-generated randomization schedule provided by the Institute of Medical Biometry and Medical Informatics, Freiburg.

General healthcare followed evidence-based, good clinical practice standards as determined by the German Agency for Quality Assurance in Medicine. German health insurance is bound by law to guarantee these standards for all citizens equally. The treatment and drug regimens of each participant were covered by insurance.

Standard of care group (SOCG)

The posttransplant immunosuppressive regimen comprised tacrolimus, mycophenolic acid, and prednisone (23). Prior to discharge, all RTR received a booklet for recording drug regimen, vital signs, and fluid balance, as well as an educational booklet (24). Additionally, a transplant nurse provided counseling, which included standardized self-management information about disease prevention, immunosuppression adherence, and self-monitoring. Thereafter, regular checkups with a resident nephrologist were combined with a best clinical practice checkup program at the UMC Freiburg. The physicians determined the time intervals between checkups according to risk stratification, and offered further consultations whenever needed. The UMC Freiburg reports provided updated diagnoses, laboratory values, and medical treatment regimen. Additional checkups with other specialists were advocated where appropriate.

Telemedically supported case management group (TSCMG)

This group received the same standard of care and telemedically supported case management. Key features are summarized in Table 1. Our aim was to apply patient-centeredness and adherence to best clinical practice. Therefore, we strived for quality, quantity, and promptness in the availability of significant information via a tailored telemedically supported case management model. The model includes three basic components: (i) a chronic case management process for the first year posttransplant; (ii) a case management process applicable for acute care situations; and (iii) a telemedically equipped team. Members comprised a transplant nurse case manager (TNCM) and two senior transplant physicians (STP: surgeon and nephrologist). All team members were employed by the UMC Freiburg. Their combined activities constituted each complete case management process, including initiation, assessment, planning, linking, monitoring, and evaluation.

Preconditions: A key factor was the consensus of the team and the medical network on patient-centered care. Figure 1 shows the collaboration structures and information pathways.

Telemedical aspects: Prior to discharge, the TNCM trained each RTR in the operation of an interactive terminal. It enabled remote telemonitoring and prompt real-time video consultations. For telemonitoring, the RTR answered standardized multiple-choice questionnaires via the terminal once a day. This included semi-open questions about fluid balance and vital signs, as well as closed-ended

Table 1: Core features and cost estimation of telemedically supported case management

Preconditions:	Consensus of personnel and medical network on patient-centered care
Overall essence, goals and strategies:	A chronic illness approach for renal transplant recipients with focus on adherence to jointly agreed goals and related medical instructions via instant expert services for individualized chronic care management and also appropriate management during acute phases in the first year posttransplant
Core activities and their providers:	Telemedically supported case management services (see below) delivered by an interdisciplinary case management team of transplant center experts
Staffing: personnel participants	• Case management team members: o2 senior transplant physicians (STP) o1 transplant nurse case manager (TNCM) • Renal transplant recipients
Materials: (recipients)	1 internal server provision (TNCM) including 1 security token (TNCM)1 laptop & 1 mobile phone (TNCM) Touchscreen terminals (STP, participants) including software licenses
Cost estimation for 23 patients:	50% TNCM position €28 500 Internal server provision €1024 Equipped team workplace €500 Extra patient-variable costs: Touchscreen terminals with software licenses × 23 €20 700 Extra infrastructure costs: €12 681 €63 405: 23 = €2757 per patient

Application of telemedical services:	Timing	Provider	Delivery	Intensity
(availability)	(8 am–2 pm on weekdays & for urgency 8 am–9 pm daily)			
• Remote telemonitoring	Every day	TNCM	Person-independent	Once daily
• Real-time video consultations with access to significant medical data at the University Medical Center for:				
o case management services	(See below)	TNCM	Person-dependent	Tailored to needs
o medical consultation/instructions	On request	STP	Person-dependent	Tailored to needs
o extra self-care-related education	On request	TNCM	Person-dependent	Tailored to needs
o extra self-management support	On request	TNCM	Person-dependent	Tailored to needs
o coaching in health-specific issues	On request	TNCM	Person-dependent	Tailored to needs
Applied methods in telemedical education, support & coaching:	Advocacy, individualization, consciousness raising, patient-driven learning, proactive information, goal setting, self-monitoring, feedback, planning coping responses, discussion, personalized-risk and scenario-based risk information			

Application of case management services:	For the chronic care situation			For a new acute care situation		
	Timing	Provider	Delivery	Timing	Provider	Delivery
(availability):	(regularly 8 am–2 pm on weekdays)			(On standby 8 am–9 pm daily)		
Process initiation	TX + 1 week	TNCM	Face-to-face	Urgency	TNCM	Mobile phone
Assessment/ reassessments	TX + 1 week/ Tailored to needs	TNCM	Face-to-face/ telemedically	Very timely after the	TNCM/ TNCM	Telemedically/ Mobile phone
Service planning/ additional planning	TX + 1 week/ Tailored to needs	STP & TNCM	Face-to-face/ telemedically	process initiation	STP/ TNCM	Mobile phone/ mobile phone
Linking to providers and care coordination	Early after planning, tailored to needs	STP & TNCM	Mobile phone, written report		STP	Mobile phone
Monitoring	Weekly to biweekly written case notes	TNCM	Telemedically, mobile phone	Every day	STP or TNCM	Face-to-face, mobile phone
Final evaluation	TX + 1 year	TNCM	Face-to-face	Patient's recovery	STP or TNCM	Face-to-face, telemedically

STP, senior transplant physician; TNCM, transplant nurse case manager; TX, transplantation.

questions about immunosuppression intake and disease-specific symptoms. The daily entry of self-measured data for telemonitoring also helped the patients form good habits.

For security, the data were transferred through a safe web-based connection. Therefore, the patient terminal was not a mobile device. Supplementary briefings were provided via calls, voice mailbox, Short Messages Services, and emails to the TNCM's mobile telephone, ensuring prompt responses. The TNCM was also equipped with a disconnected security token that allowed 24-h online access to all significant medical data at the UMC Freiburg. Device codes, user codes, passwords, and firewalls ensured overall protection.

Case management aspects: We followed the recommendations from the German Association for Care and Case Management (DGCC) (25), supplemented by provision of direct medical services tailored for RTR.

The chronic care case management process started for each RTR at hospital discharge. After assessment, the TNCM provided planning, linking,

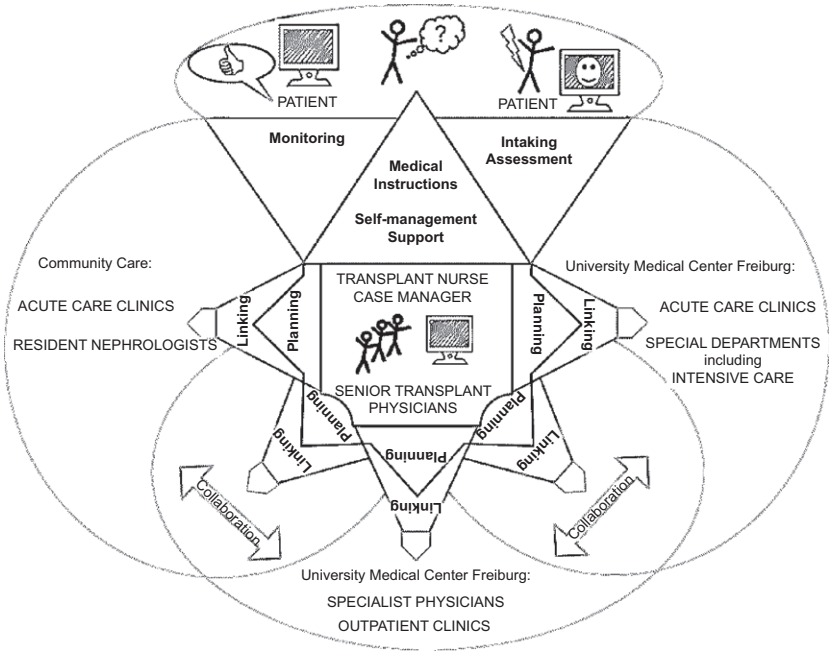

Figure 1: Collaboration structures and information paths in the case management processes for living-donor renal transplant recipients.

and monitoring for the achievement of jointly agreed medical goals, underpinned by self-management and self-care-related actions. The RTR had continuous access to an expert to discuss how to deal with specific challenges, and how to set informed health-protection priorities in daily living. The TNCM also provided additional support and linking, if necessary. Furthermore, the TNCM regularly assessed details received via telemonitoring, video consultations, and mobile phone, and bridged communication between the RTR and the STP. The STP obtained significant details and cooperated closely with the resident nephrologists.

In emerging acute care situations, the TNCM triggered the second case management process. The TNCM provided a precise synopsis of all medically significant details to one of the STP immediately after assessment, enabling the STP to plan provision of instant interventions precisely tailored to the individual's needs. If necessary, timely video visits with the STP were organized. The STP either provided medical instructions, initiating direct treatment at the UMC Freiburg, or arranged prompt linking to treatment by another specialist within the collaborative framework (Figure 1).

Variables and measurements

The study variables included medical outcomes, adherence, quality of life, and costs. Table 2 summarizes research hypotheses, target outcomes, and measurements.

Data are reported at 0, 3, 6, and 12 months posttransplant. At each time point, a resident physician and a UMC Freiburg clinician estimated the RTR's adherence to the immunosuppressive regimen and provided collateral reports on an ordinal scale. A trained psychologist assessed self-reports using the (i) Basel Assessment Adherence to Immunosuppression Scale (BAASIS®), (ii) health-related "Fragebogen Alltagsleben" (ALL), (iii) disease-specific End-Stage Renal Disease Symptom Checklist-Transplantation Module (ESRD-SCL™), and (iv) Brief Symptom Inventory 18 (BSI-18). These instruments are all standardized and reliable, and have been validated for use in RTR populations (26–34). The RTR answered a closed-ended question about their working time percentage. Finally, the tacrolimus trough level and transplant function were documented. Medical staff collected the reports from each treating physician and assessed them meticulously regarding the "hard" target outcomes.

For cost determination, the division for finance and control of the UMC Freiburg assigned the patient's unplanned admission diagnoses to the German diagnosis-related group (DRG) fixed-price system with an average length of stay, the lowest patient clinical complexity level, and standardized base rates valid throughout Baden-Württemberg, Germany (19).

Regarding assessment of nonadherence, we adopted the definition of the "Consensus Conference" on nonadherence to immunosuppressants (35) as a "deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect." Likewise, we followed their recommendations for assessment of nonadherence with a CAS, each of which consisted of one self-report, two clinician reports, and one tacrolimus assay (21,35). Nonadherence was determined using the pre-defined CAS cut-off system of Schäfer-Keller et al. (21). No data were included following graft loss. To describe the dynamics of nonadherence, we further compiled a CAS percentage grading as an interval rating scale, and transcoded it to the definition of nonadherence (35). Table 3 shows the corresponding scheme.

Data analyses

Statistical analyses were performed in cooperation with the Center for Medical Biometry and Medical Informatics, University of Freiburg. The Shapiro–Wilk test verified that most parameters were not normally distributed and therefore ANOVA-type statistics (ATS) by Brunner in F1-LD-F1 design (36) were applied using R statistical software version 3.0.0 © (https://www.r-project.org; R Foundation for Statistical Computing, Vienna, Austria) (37), and package nparLD version 2.1 (Free Software Foundation, Inc., Boston, MA) (38). ATS is suitable for rank-based, nonparametric,

Table 2: Hypotheses, outcomes, and measurement for effect determination of the telemedically supported case management group (TSCMG) compared to the standard of care group (SOCG)

Research hypotheses	Target outcomes	Measurement instruments and means
Regarding acute care situations, TSCMG and SOCG are different in terms of:		
	PRIMARY:	
Unplanned inpatient hospitalization	Unplanned admission rate	Sum of unplanned admissions according to all medical reports
	SECONDARY:	
Unplanned prolonged inpatient hospitalization	Length of unplanned stay	Sum of unplanned inpatient days according to all medical reports
Unexpected costs for inpatient care	Unplanned inpatient care costs in Euros (€)	Sum of unplanned inpatient care costs according to the diagnosis-related groups (DRG) fixed-price system in Germany
Acute rejection risk	Rejection rate	Sum of biopsy-proven acute rejections
Treatment for acute rejections	Length of time before rejection therapy initiation	Sum of days between first creatinine level increase before a biopsy-proven rejection and the start of glucocorticoid therapy according to the patient charts
Preservation of graft function	Estimated glomerular filtration rate (eGFR)	Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations with serum creatinine level in medical reports
Real-life ambulatory care visits	Ambulatory care visit rate	Sum of ambulatory care visits (outpatient clinic and resident physicians) according to all physician reports
Regarding the chronic care situation, TSCMG and SOCG are different in terms of:		
Immunosuppressive regimen adherence	Composite adherence score (CAS) and CAS percentage grade	• Self-Report in the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS®) • Collateral reports (physicians, nurses) • Hit of target tacrolimus trough levels
Quality of life	Psychological and quality-of-life-questionnaires' subscale scores	• Fragebogen Alltagsleben (ALL) • End-Stage Renal Disease Symptom Checklist-Transplantation Module (ESRD-SCL™) • Brief Symptom Inventory 18 (BSI-18)
Return to employment	Working time percentage	Closed-ended question about working time percentage

Table 3: Prespecified adherence percentage grading scheme for tacrolimus trough level, collateral report, and self-report

Percentage grading	Collateral report	Tacrolimus trough level (ng/mL)	Self-report	Transcoding to nonadherence
100%	1 (excellent)	(4.5–9.0)	Adherence in every aspect	Fully adherent
90%	1.5	(9.1–9.2)	Adherence in every aspect and lacking memorization of the regimen doses	Fully adherent
80%	2 (good)	(9.3–9.5)	Adherence except for timing once	Partial adherent
70%	2.5	(9.6–9.7)	Adherence except for timing once and lacking memorization of the regimen doses	Partial adherent
60%	3 (fair)	(9.8–10.0)	Adherence except for taking once	Nonadherent
50%	3.5	(10.1–10.2)	Adherence except for taking once and lacking memorization of the regimen doses	Nonadherent
40%	4 (poor)	(10.3–10.5)	Self-reported timing non-adherence more often than once	Nonadherent
30%	4.5	(10.6–10.8)	Self-reported drug holidays	Nonadherent
20%	5 (very poor)	(10.9–11.0)	Self-reported independent dose reductions	Nonadherent
10%	5.5	<4.5 or >11.0	More than one aspect of nonadherence	Nonadherent

repeated-measures analyses and permits the covariance matrix to be singular. It provides reliable results for small sample sizes and data with outliers (36). p-values ≤ 0.05 were deemed statistically significant.

All other tests were performed with IBM SPSS Statistics 22.0 (IBM Corp, Armonk, NY). The proportion of patients showing nonadherence was compared between groups using a two-tailed Fisher exact test. For post-hoc tests, two-tailored Mann–Whitney U-tests, Friedman rank sum tests, and pairwise Wilcoxon signed-rank tests were applied. Post-hoc test p-values were adjusted with Holm's sequential Bonferroni procedure (39). Effect sizes for post-hoc tests were calculated with Cohen's $r = \frac{z}{\sqrt{N}}$ (40).

We used a 2 × 4 design with treatment (TSCMG, SOCG) and post-transplant time point in months (0mo = baseline assessment at time

point T1, 3mo = T2, 6mo = T3, 12mo = T4). P-values and corresponding ATS are presented as F (df, ∞), with df as numerator degrees of freedom (N). For two-tailed post-hoc tests, median, interquartile range (IQR); test value U (Mann-Whitney U-test) or Z (Wilcoxon rang sum test), p-value, and Cohen's measure r as effect size are provided. A sensitivity power analysis using G*Power 3.1.7 (41) showed that for the sample size of N = 46, an alpha level of 0.05 and a probability of 0.80, a two-tailed Mann-Whitney U-test would be able to detect effect sizes larger than Cohen's d = 0.84 (5), respectively Cohen's r = 0.38 [$r = \frac{d}{\sqrt{d^2+4}}$] (42).

Results

Of 56 eligible participants, 5 did not speak German and 1 died before allocation. Two patients in each group did not agree to concealed allocation and declined participation before allocation. One TSCMG participant subsequently refused ongoing telemonitoring and two participants finished the SOCG after graft loss, although their follow-up visits were completed. Forty-six valid datasets were available for an intent-to-treat analysis at the end of the data collection period (Figure 2), which took place between October 2011 and April 2014.

At baseline assessment, characteristics were comparable between the two groups (Table 4). A detailed clinical description is provided elsewhere (22).

Results regarding acute care situations

The TSCMG and SOCG differed in their unplanned inpatient hospitalization rate. There was a significant main effect for treatment, F (1, ∞) = 7.71, p = 0.006, and a significant interaction F (1.7, ∞) = 4.41, p = 0.017. Post-hoc analyses showed that the TSCMG had significantly fewer unplanned admissions at T3 and T4. At 12 months

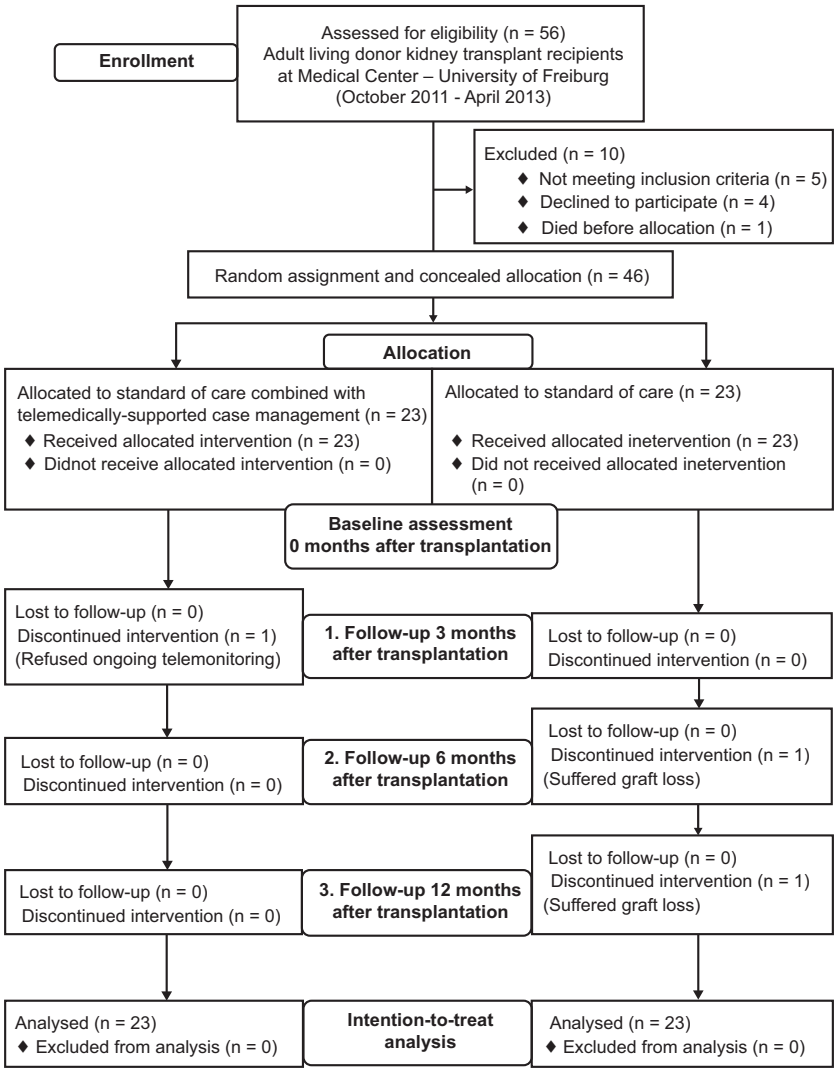

Figure 2: Flow diagram of the recruitment and data collection process in a repeated-measure design.

Table 4: Study sample characteristics at baseline assessment

	Telemedically supported case management group n = 23	Standard of care group n = 23	P-value
Age (years), median (range)	46 (18–59)	51 (19–66)	0.23[1]
White, n (%)	23 (100)	23 (100)	1.00[2]
Male, n (%)	14 (61)	11 (48)	0.55[2]
Living with partner, n (%)	19 (83)	18 (78)	1.00[2]
Employed, n (%)	17 (74)	14 (61)	0.53[2]
Living-related donor, n (%)	9 (39)	12 (52)	0.57[2]
ABO-incompatible, n (%)	7 (30)	6 (26)	1.00[2]
Serious posttransplant complications, n (%)	11 (48)	12 (52)	1.00[2]
Number of drugs to take, median (range)	9 (6–13)	9 (6–17)	0.38[1]
Daily immunosuppression intake, median (range)	2 (2)	2 (2)	1.00[2]

[1]Mann–Whitney U test.
[2]Fisher's exact test.

posttransplant: TSCMG (median = 0 admissions, interquartile range [IQR] = 1) versus SOCG (median = 2 admissions, IQR = 2), U = 132.5, p = 0.002, r = 0.44.

Additionally, the TSCMG had fewer unplanned prolonged inpatient hospitalizations with a significant main effect for treatment, F (1, ∞) = 6.59, p = 0.01; and a significant interaction, F (1.7, ∞) = 3.8, p = 0.029. The post-hoc analyses revealed a shorter length of unplanned stay for the TSCMG at T3 and T4. At 12 months posttransplant: TSCMG (median = 0 days, IQR = 6) versus SOCG (median = 13 days, IQR = 23), U = 141.0, p = 0.005, r = 0.41.

The rate and length of unplanned hospitalizations at T2 were comparable to T3 and T4 for the TSCMG, while unplanned hospitalization in the SOCG increased significantly at each time point (T). For unplanned admissions, T2 until T3 and T3 until T4 were both Z = 2.74, p = 0.004, r = 0.40. For length of unplanned stay, T2 until T3 and T3 until T4 were both Z = 2.81, p = 0.002, r = 0.41. Figure 3 illustrates the interaction of treatment and time effects regarding unplanned hospitalizations by group means.

Fewer admission rates and shorter lengths of unplanned hospitalization in the TSCMG were observed for almost every diagnosis (Table 5), which was reflected in inpatient care savings of €3417 per patient.

The SOCG suffered two graft losses (acute humoral rejection, hemorrhage of a native kidney), the TSCMG none. Biopsy-proven acute rejection rates (Table 5) were too low for permit comparative analyses. Differences in ambulatory care visit rates did not reach statistical significance at 12 months posttransplant (TSCMG: median = 43 visits, IQR = 22. SOCG: median = 45 visits, IQR = 28), U = 216.5, p = 0.297. Both groups maintained transplant function: the median difference for the change in estimated GFR between T1 and T4 was +3.6 mL in TSCMG versus +0.6 mL in SOCG.

Results regarding the chronic care situation

Nonadherence was observed in 56.5% of the SOCG compared to 17.4% of TSCMG participants (p = 0.013). The TSCMG and the SOCG also differed in their median CAS percentage grading scores, with a significant main effect for treatment, F (1, ∞) = 23.17, p = <0.001; and a significant interaction, F (2.6, ∞) = 10.58, p < 0.001. Post-hoc analyses revealed significant differences at all time points. The group comparison at 12 months posttransplant showed the following: TSCMG (median =

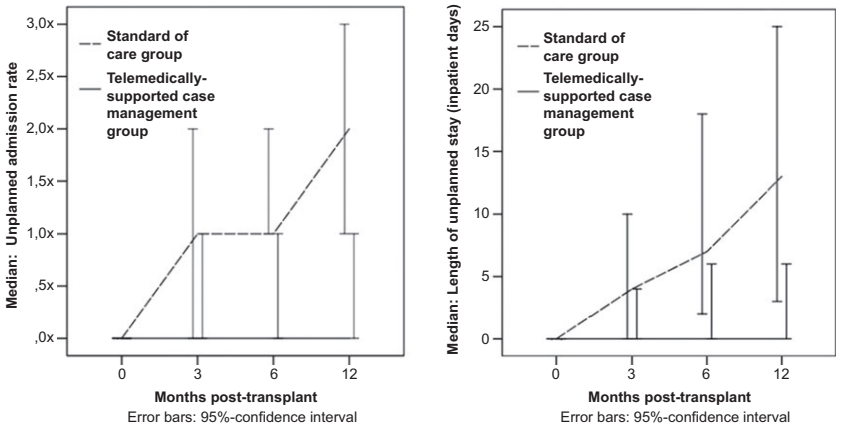

Figure 3: Treatment and time interaction effects regarding unplanned admission rates and length of unplanned stay (inpatient days) per year.

Table 5: Differences in number of unplanned admissions and length of unplanned inpatient care

	12 months posttransplant		
	Total of admissions (total of inpatient days)		
Reasons for unplanned admissions	Standard of care group (n = 23)	Telemedically supported case management group (n = 23)	Differences in length of unplanned inpatient care
Acute rejection	2 × (73)	1 × (17)	1 × (56)
Postrenal azotemia	10 × (71)	4 × (15)	6 × (56)
Urinary tract infection	10 × (70)	6 × (27)	4 × (43)
Enteral infection	6 × (40)	1 × (6)	5 × (34)
Cytomegalovirus infection	3 × (37)	1 × (22)	2 × (15)
Pulmonary infection	4 × (23)	0 × (0)	4 × (23)
Drug-induced leucopenia	2 × (25)	1 × (7)	1 × (18)
Infection of unclear focus	2 × (13)	0 × (0)	2 × (13)
Abdominal abscess	3 × (49)	2 × (39)	1 × (10)
Cardiac arrhythmias	2 × (5)	0 × (0)	2 × (5)
Kidney hemorrhage	1 × (5)	0 × (0)	1 × (5)
Acute tubular necrosis	1 × (4)	0 × (0)	1 × (4)
Drug-induced renal failures	2 × (7)	2 × (5)	0 × (2)
Ischialgia	0 × (0)	1 × (1)	−1 × (−1)
Total	48 × (422)	19 × (139)	29 × (283)
Median	2 × (13)	0 × (0)	
Interquartile range	6 (23)	2 (6)	

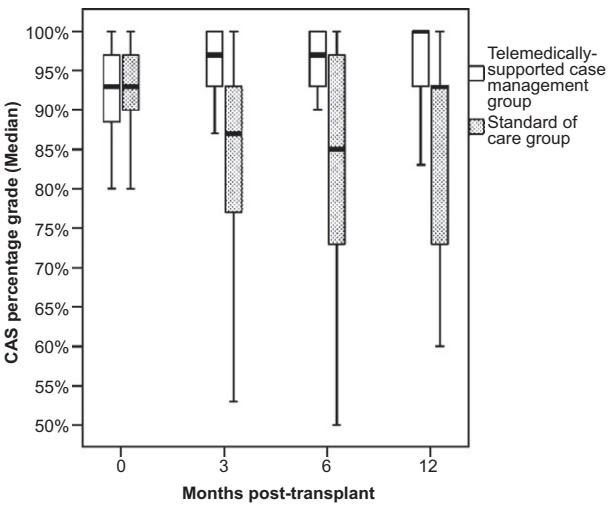

Figure 4: Levels of adherence performance, dynamics, and variability. The lower the median CAS percentage grade, the poorer the estimated adherence to the immunosuppressive regimen. Median values are shown as a band in the box plots.

100%, IQR = 7) versus SOCG (median = 93%, IQR = 21.5), U = 71.5, $p < 0.001$, r = 0.62.

Figure 4 presents the changes in CAS percentage grading over time. The median CAS percentage grading for the TSCMG was always above 97%, and was 100% at T4, whereas the SOCG score fluctuated between 85% and 93%. Full adherence (Table 3) at all points was only achieved in the TSCMG. Adherence throughout follow-up was demonstrated by 60.9% of patients in the TSCMG versus only 8.7% of patients in the SOCG. In all other participants, adherence showed at least some fluctuation during the first year posttransplant.

In both groups, psychological distress (BSI-18) decreased and health-related quality of life (ALL) improved significantly over the first year posttransplant. Regarding disease-specific quality of life (ESRD-SCL^{TM}), the TSCMG and SOCG differed on two subscales: (i) cardiac and renal dysfunction, and (ii) side effects of corticosteroids. Figure 5 illustrates that in the TSCMG group, corticosteroid side effects and cardiac and renal dysfunction, decreased significantly at every time point and progressively approached zero. The scores differed from the SOCG most significantly at (i) T3 (TSCMG [median = 0.14, IQR = 0.29] versus SOCG [median = 0.29; IQR = 0.43], U = 132.5; p = 0.004, r = 0.42) and (ii) T4 (TSCMG [median = 0, IQR = 0.2] versus SOCG [median = 0.4, IQR = 0.6], U = 133, p = 0.004, r = 0.42).

The TSCMG cohort returned to full employment soon after discharge, as indicated by their median working time percentages, which remained stable throughout year 1 posttransplant. The SOCG differed significantly between the baseline assessment (median = 50%, IQR = 100) and month 3 posttransplant (median = 0%, IQR = 50), Z = 2.694, p = 0.006, r = 0.4, and did not return to full employment within the first posttransplant year (Figure 6).

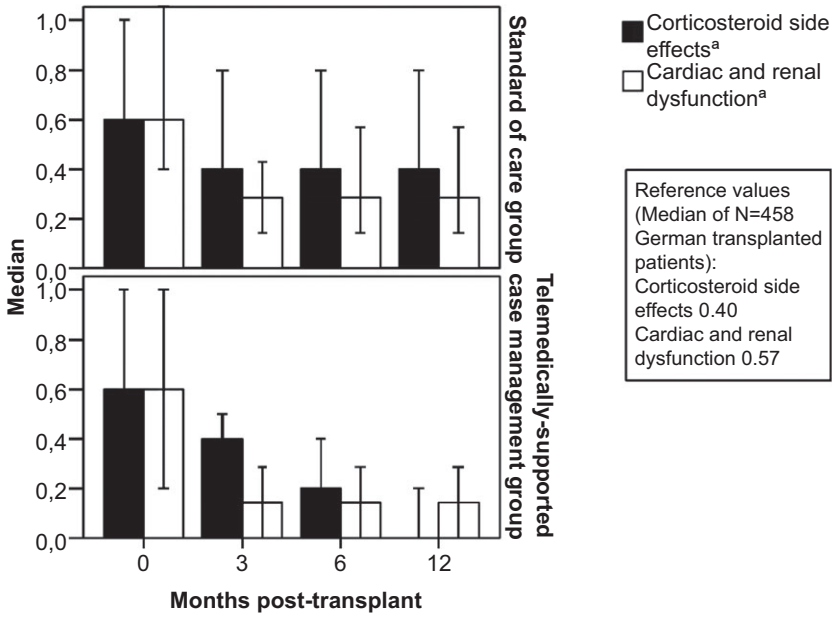

Figure 5: Corticosteroid side effects and cardiac and renal dysfunction. [a]Subscale of the End-Stage Renal Disease-Symptom-Checklist-Transplantation Module (ESRD-SCL^{TM}).

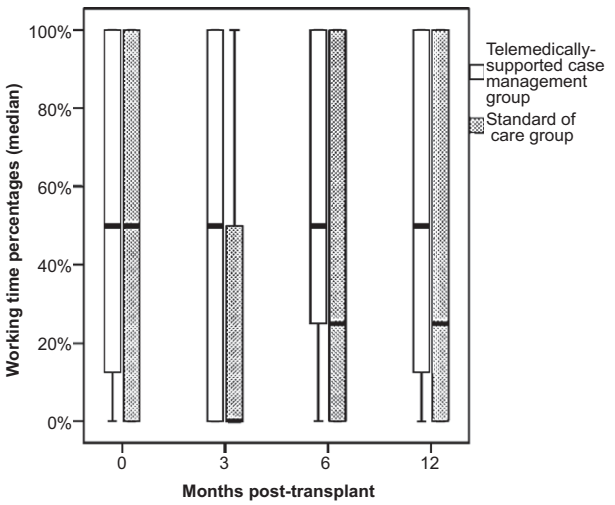

Figure 6: Working time percentages. Median values are shown as a band in the box plots.

Discussion

Combining telemedicine and case management during the first year posttransplant is a novel strategy. These results confirm that the combination is effective in optimizing evidence-based aftercare. The approach is interdisciplinary and the judicious interplay of all parties improved medium-term outcomes at the patient level. The TSCMG and the SOCG differed significantly in outcomes regarding both acute and chronic care situations.

Of pivotal importance for acute care was interactive access to an expert team who provided verbal assurance and physical assistance. The amount of additional contact time differed between cases, but the needs of all 23 RTR were adequately met within the usual STP job profile combined with an extra 50% of a TSCM staff member. Prompt support and targeted actions helped avoid the development of serious complications, and were available on evenings and weekends when standard facilities were not easily accessible (Table 1). Most admission diagnoses resulted in a shorter length of unplanned stay or prevented acute inpatient care entirely. One would expect unplanned hospitalization rates to stabilize after month 3 because of lower rejection risk and less intensive immunosuppression, but this was observed only for the TSCMG. The interaction of time and treatment effects with an increasing sequence of group differences over time indicates efficiency. Both aftercare strategies resulted in a low rate of acute rejection and stable graft function. The inpatient care and costs in the two groups, however, differed considerably: the 23 RTR in the SOCG were hospitalized 29 times more often and spent 283 days longer in inpatient care, with correspondingly greater costs. Differences in ambulatory healthcare visits between groups did not reach statistical significance, suggesting that the effectiveness of telemedically supported case management was the only meaningful variable in patient care.

Nonadherence to the immunosuppression regimen was significantly less prevalent, and less variable, in the TSCMG group versus the SOCG group, with a large

effect size (Cohen's r > 0.60). The TSCMG group experienced benefits in disease-specific quality of life in terms of lower cardiac and renal dysfunction, and corticosteroid side effects. Compared to a reference group of 458 German RTR in whom the median score for corticosteroid side effects was 0.4 (31), the SOCG scored the same while the TSCMG had a score of 0.0 at T4. The effect size was moderate (Cohen's r > 0.4). Overall, the SOCG appears to have had suboptimal adaptation processes, as indicated by the failure to return to full employment during the first year posttransplant while the TSCMG managed both a full and an early return.

Starting early, at posttransplant discharge, is rational because this is a natural point of realignment for patients. The study results suggest that within the first 3 months, the SOCG and the TSCMG progressed differently in terms of self-management and self-care, as well as in self-responsibility for their disease-specific status, a modus operandi that was then maintained. A chance for optimal development appeared to have been missed in the SOCG group by year 1.

The TSCMG exploited the opportunities afforded by the program. First, applying various different recognized chronic care methods contributed to the successful outcomes. Second, instant, individualized transplant-centered expert support was consistently available when particular challenges arose, facilitating ideal, patient-driven learning situations. The focus shifted to successfully overcoming barriers and being able to ensure adherence. Third, the success of this telemedical concept is founded on the personal attributes of the team. Written feedback from patients elicited spontaneous comments praising the experience, competency, steadiness, reliability, security, comprehensiveness, and the personalized approach. This may explain why almost every patient was fully engaged throughout the first year posttransplant, with the designed intervention being implemented without difficulty. A further contribution might be the human element underpinning videoconferencing, and that the touch-screen terminals were found to be easy to use. Some patients would have appreciated tablets with software for mobile telemonitoring and video consultation, but understood that German data protection laws were a barrier to their use.

The TSCMG achieved improved outcomes during the intervention, but whether the benefits of telemedically supported case management are sustained long term remains unclear, an important limitation of this study. We therefore plan to evaluate the study sample at 5 years posttransplant. A second limitation is that the intervention is not proven for different types of RTR. Therefore, we have started evaluating telemedically supported case management for combined pancreas–kidney and for deceased-donor kidney transplant recipients. Third, the findings cannot necessarily be generalized because of the small sample size and the fact that this was a single-center study. In addition, patients and physicians were not blinded. However, all treating physicians naturally set a priority for the best possible, noncompetitive outcome for every RTR. To control further selection biases, we used randomization and concealed allocation. We took care to use validated, reliable, and standardized means for measurement (26–34) and data were partly assessed externally. Because of the absence of a "gold standard" for assessment on nonadherence, we sought to maximize the sensitivity and accuracy of the measurement (21,35).

After completing the study, the UMC Freiburg adopted the approach and provided a part-time (50%) TNCM position. A thorough budget impact analysis, the details of which would exceed the scope of this report, indicated that the intervention could be implemented in medium- and high-volume transplant centers. We would anticipate the results reported here to be replicable in higher patient numbers if the nurse support time was scaled up accordingly. The current reimbursement practice may be the main hurdle for implementation.

This is the first randomized, controlled trial to evaluate telemedically supported case management. Application of this approach was associated with medical, disease-specific, and social advantages at the patient level, as well as cost savings for health payers. This comparative effectiveness research has demonstrated the potential of telemedically supported case management to optimize routine evidence-based posttransplant aftercare and support its application at tertiary care hospitals. It provides a basis for a multicenter randomized trial to verify these outcomes in the medium and long term.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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